CaP CURE Initiatives and Projects

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CaP CURE was founded in 1993 to help find better treatments and a cure for prostate cancer. By reducing the time and complexity required to apply for funding, and by funding many first-time applicants, CaP CURE has attracted a large number of high-level investigators to the field of prostate cancer research. The organization's Therapy Consortium meets regularly to address major issues that impede progress in clinical development of new treatments for prostate cancer. CaP CURE has also sponsored an initiative to standardize clinical trial design scenarios for the clinical state of rising prostate-specific antigen and intends to present them to the Food and Drug Administration in partnership with the National Dialogue on Cancer. Finally, CaP CURE's efforts have resulted in a significant increase in federal funding of prostate cancer research programs.
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CaP CURE, also known as The Prostate Cancer Foundation, was founded in 1993 by philanthropist and financier Michael Milken and his family. The mission of CaP CURE is to eradicate prostate cancer as a health risk for men and their families. In 1993, prostate cancer research was not a priority for the National Cancer Institute (NCI) or for the research community in general. Several strategic programs were created by CaP CURE to bring about dramatic changes

Table 1
Selected Results from CaP CURE Program

Fund Recipients	Affiliation	Research Results
Warren Heston, PhD Neil Bander, MD	Cleveland Clinic (formerly of Memorial Sloan-Kettering Cancer Center) Cornell Medical School	Discovered PSMA, developed experimental monoclonal antibodies to PSMA, and advanced anti-PSMA antibodies into the clinic for the treatment of advanced prostate cancer. Millennium Pharmaceuticals is developing this antibody
Joel Nelson, MD Michael Carducci, MD	University of Pittsburgh (formerly of Johns Hopkins University) Johns Hopkins University	Demonstrated the involvement of the endothelin axis in prostate cancer within bone and stimulated the development of endothelin antagonists for the treatment of advanced prostate cancer
Jonathan Simons, MD	Emory University (formerly of Johns Hopkins University)	Developed a prostate cancer vaccine composed of prostate cancer cell lines transduced to express immune-stimulating cytokines. This vaccine is under development by Cell Genesys for the treatment of advanced prostate cancer
Gerald Murphy, MD (deceased)	Northwest Hospital	Developed methods and advanced to the clinic a variety of dendritic cell vaccines for the treatment of advanced prostate cancer. Dendreon and Northwest BioTherapeutics as well as numerous academic investigators continue to develop these vaccines
Matthew Smith, MD, PhD	Massachusetts General Hospital	Studied the effect of androgen-deprivation therapy on bone loss and the ability of bisphosphonates to prevent such loss. This work led to the recent FDA approval of zoledronic acid for the treatment of prostate cancer in bone
Neal Rosen, MD, PhD	Memorial Sloan-Kettering Cancer Center	Characterized and developed a class of anticancer drugs that inhibit HSP90 and induce the cellular degradation of many important components of signal transduction pathways. The prototype in this series of compounds is a derivative of geldanamycin, which is being developed at Sloan-Kettering

PSMA, prostate-specific membrane antigen; FDA, Food and Drug Administration; HSP, heat shock protein.

in the prostate cancer research landscape. Following a venture-style model, CaP CURE funds a diverse array of promising, early-stage research projects and has provided more than $120 million to 1100 critical research projects in 100 research centers around the world. The purpose of this article is to describe the CaP CURE strategy in the context of the vast accomplishments achieved in the field of prostate cancer research in the past decade.

Stimulation of the Field

The single largest problem facing prostate cancer research in 1993 was lack of a critical mass of top-level investigators working in the field. CaP CURE initiated a two-pronged effort to solve this problem. The first strategy was to stimulate the field with leveraged research awards and to begin aggregating a critical mass of diverse and expert investigators. The second strategy involved influencing the federal government and will be discussed later.

CaP CURE initiated a novel competitive research award program to simplify the funding process for people working in the field. Specifically, CaP CURE aimed to reduce the time and complexity required to apply for funding and report results. The institution of a five-page proposal requirement streamlined the application process in contrast to the typically massive applications required by the National Institutes of Health (NIH)

and other government sources of funding. The time from submission to money-in-hand was reduced to 90 days. The reporting of results was reduced to a 6-month progress report letter and a presentation at the end of the year's funding period at the CaP CURE Annual Scientific Retreat.

Since its inception ten years ago, CaP CURE has awarded over 800 competitive research awards. A few notable results from this program are shown in Table 1. By no means does Table 1 present an exhaustive list of contributions that were seeded by CaP CURE nor do we intend to take total credit for these successes. Nonetheless, these contributions provide examples of the way in which the rapid, venture-style research awards provided by CaP CURE and how they advanced the field in unique ways.

Another interesting way to assess the impact of CaP CURE on the discovery and development of new drug candidates for advanced prostate cancer is to examine the number of drugs in development over time and the number of drug-development programs funded by CaP CURE. A systematic comparison of these figures in 1997 versus 2003 reveals a dramatic change (Figure 1). The number of prostate cancer drugs in clinical trials has increased 50%, from 91 to 139, in the past 5 years. Of the phase I and II programs in 2003, 39% were influenced by CaP CURE either through direct funding or initiation of research by a CaP CURE Therapy Consortium member.

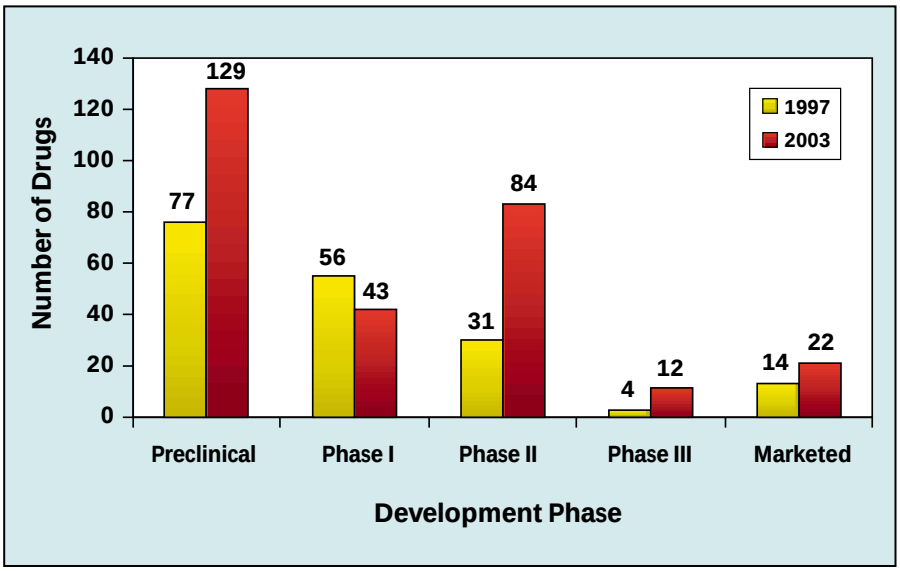

Figure 1. *Prostate cancer drugs in development, 1997 versus 2003.*

While phase III programs still mainly involve improved hormonal therapies, phase II programs contain a marked increase in the investigation of mechanism-based drugs and other novel therapies. Much hope for the future is engendered by these new experimental treatments for advanced prostate cancer.

The additional important dimension to the CaP CURE competitive research awards program is the attraction of new scientists to the field of prostate cancer research. To stimulate a high level of interest in the field, nearly half of these awards each year go to people who have never applied to CaP CURE in the past. A representative list of these recipients is shown in Table 2.

Since 1993, CaP CURE has awarded 817 competitive research awards totaling $89.1 million.

Finally, CaP CURE has supported the careers of beginning physicians and scientists through Young Investigator Awards. A total of 19 individuals received this three-year award to help bridge them to their first support. These investigators form the core of the next generation of prostate cancer researchers.

The CaP CURE Therapy Consortium

The CaP CURE Therapy Consortium is composed of medical oncologists representing eight centers across the United States. Members of the current group are listed in Table 3. The Therapy Consortium meets regularly to address major issues that impede progress in clinical development of new treatments for prostate cancer. Major contributions and activities of the group include:

- Establishing taxane-based chemotherapy as a treatment option for advanced prostate cancer
- Acting as an "uncooperative" cooperative group to plan new academic and industrial trials for new prostate cancer treatments
- Screening new drugs and targets for inclusion in trials
- Participating in clinical-trial standardization programs
- Working together to select a clinical research informatics system to automatically capture and process scientific and clinical research

Table 2
First-Time Recipients of CaP CURE Funding

Fund Recipient	Affiliation	Contributions/Research Area
K.C. Nicolau, PhD, synthetic organic chemist	Research Institute of Scripps Clinic	Synthesized cytotoxic compounds discovered as novel natural products from marine organisms
Pinchas Cohen, MD, pediatric endocrinologist and expert in axis in cancer	University of California, Los Angeles	Has made significant contributions in his studies of the insulin-like growth factor axis in prostate cancer
Robert Fletterick, PhD, biophysicist	University of California, San Francisco	Funded to focus his structural biochemistry expertise on the androgen receptor in prostate cancer and to discover novel androgen receptor antagonists
Owen Witte, MD, expert in cellular biochemistry	University of California, Los Angeles	Has applied his expertise in stem cell biology to the prostate cancer problem and has organized a significant body of prostate cancer research at UCLA involving researchers from numerous groups
John Reed, MD, expert in apoptosis	Burnham Institute	Has directed a significant amount of his research effort toward prostate cancer

results and link the participating centers.

The CaP CURE Gene and Family Studies Consortium

As can be seen in Figure 2, prostate cancer has the strongest familial linkage among all major cancers. A man with one relative diagnosed with this deadly disease has more than twice the normal risk of developing prostate cancer. With two relatives, the risk increases five-fold. With three or more relatives, the risk of getting prostate cancer is close to 100 percent. The CaP CURE Gene and Family Studies Consortium, pursued under the leadership of Drs Janet Stanford, Elaine Oestrander, Leroy Hood, Owen Witte, Charles Sawyers, and William Catalonia, funded the collection of the largest cohort of families with multiply affected prostate cancer survivors among first-degree relatives. As a result of this program, genomic regions were discovered that were associated with these multiply affected families. However, the identification of a responsible gene from this study, and for all prostate cancer family studies, remains elusive.

Clinical Trial Design Initiative

CaP CURE has sponsored a significant effort, through the leadership of Howard Scher, MD, to create and standardize clinical trial design scenarios in the clinical state of rising prostate-specific antigen (PSA). A working group comprising investigators from the National Cancer Institute (NCI), the U.S. Food and Drug Administration (FDA), academia, and

Table 3
CaP CURE Therapy Consortium Members

Center	Participant
Dana-Farber Cancer Institute	Philip Kantoff, MD
Memorial Sloan-Kettering Cancer Center	Howard Scher, MD
Johns Hopkins University	Mario Eisenberger, MD; Mike Carducci, MD; Bill Nelson, MD, PhD
University of Wisconsin	George Wilding, MD
University of Michigan	Ken Pienta, MD
M.D. Anderson Cancer Center	Chris Logothetis, MD
Cedars-Sinai Health Science Center	David Agus, MD
University of California, San Francisco	Eric Small, MD

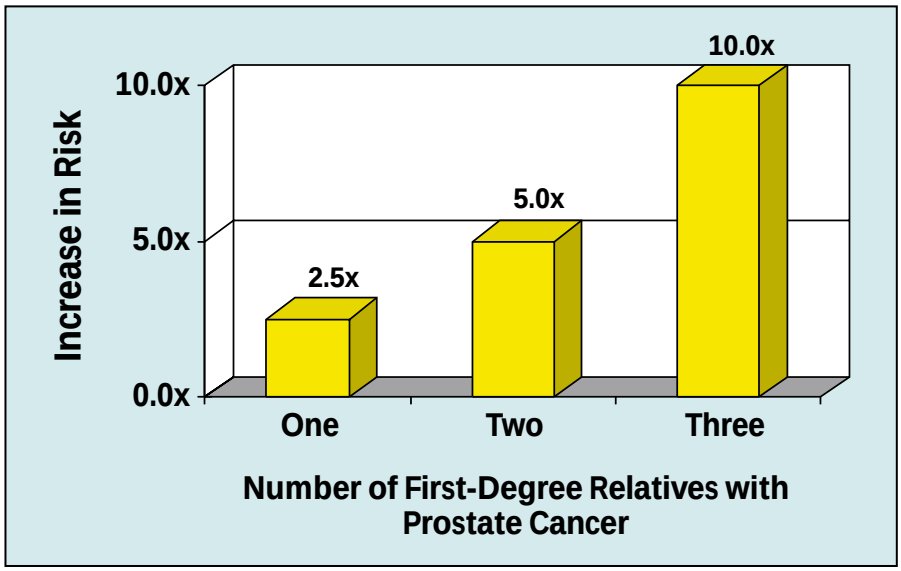

Figure 2. *Increase in an individual's risk of developing prostate cancer by number of first-degree relatives with the disease. Data from Carter et al.*[1]

industry has been building consensus in this area for the past 2 years. The group is very close to submitting a manuscript for publication. This work used the NCI PSA consensus recommendations as a point of departure in the development of a comprehensive and streamlined set of trial designs.

This effort involves the CaP CURE–funded work of Anthony D'Amico, MD, PhD. Dr D'Amico recently demonstrated that PSA doubling time following primary treatment failure is a surrogate for death due to prostate cancer.[1] His current work focuses on mining large, well-characterized databases of prostate cancer patients to determine if reduction in PSA (ie, a treatment effect) is a surrogate for outcome. Top-level statistical experts are collaborating on this very early effort. CaP CURE is also funding a retrospective collection of prostate cancer outcome data at the University of California, San Francisco (Mack Roach, MD) and Johns Hopkins University (Alan Partin, MD, PhD). We believe that these databases hold clues to predicting outcome for prostate cancer in ways that will help us responsibly complete clinical development of new drugs in less time.

Finally, we hope to present these streamlined trial design paradigms to the FDA in partnership with the National Dialogue on Cancer (NDC). The NDC is a forum that brings together the principal leaders of key national cancer organizations, agencies, and institutions, plus central figures from other public, private, and nonprofit entities, to foster and support efforts to overcome cancer. Participants in the NDC include the heads of federal and state governmental agencies; private organizations, such as pharmaceutical companies and the motion picture industry; and nonprofit groups whose missions relate to cancer research, control, and/or patient advocacy. Other individuals with a deep concern about cancer who have achieved prominence in the entertainment, news, and other industries are also engaged in the NDC. There are about 150 NDC participants. Former President George Bush and Barbara Bush are Co-chairs of the NDC, with Senator Dianne

Main Points

- CaP CURE is an organization founded in 1993 to find better treatments and a cure for prostate cancer.
- CaP CURE has stimulated the field of prostate cancer research by streamlining its funding process and awarding nearly half of its grants to first-time applicants.
- The number of prostate cancer drugs in clinical trials has increased markedly in the last 5 years, and 39% of phase I and II trials of prostate cancer drugs in 2003 were influenced by CaP CURE funding.
- Among other activities, the CaP CURE Therapy Consortium screens new drugs and targets for inclusion in trials and participates in clinical-trial standardization programs.
- CaP CURE has sponsored a major effort to develop a comprehensive and streamlined set of trial designs and, with the National Dialogue on Cancer, hopes to influence the Food and Drug Administration to accept these design paradigms before the end of 2003.
- Through CaP CURE's efforts, federal funding of prostate cancer research has increased significantly, from $25 million to more than $500 million, enabling the development of important research programs throughout the country.

Feinstein serving as Vice Chair. We will seek to engage this group to help us influence the FDA to accept our supportable trial design scenarios before the end of 2003.

Increase in Federal Government Funding of Prostate Cancer Research

The NIH and NCI funded approximately $23 million of prostate cancer research in 1993. CaP CURE effected great change in this deficiency through lobbying and increasing societal awareness. In 2003, we should see an approximately 25-fold increase in prostate cancer research funding by the federal government. Within this significant increase in funding are the following federal programs:

- NCI prostate cancer Specialized Program of Research Excellence (SPORE) grants
- Department of Defense Prostate Cancer Research Program grants
- Novel NCI programs such as Quick Trials and Rapid Access to Intervention Development (RAID)

This significant level of funding has created a stable basis for development of important programs in prostate cancer research at many centers across the nation. We believe that CaP CURE–funded programs help investigators leverage the immense government resources afforded through NCI, NIH, and the Department of Defense. In fact, the best outcome for a CaP CURE–funded research program is to compete successfully for a large government grant that will enable research to move closer to or into the clinic.

Summary

The horizon for prostate cancer research and progress has never been brighter. A group of superior physicians and scientists is working together to solve the problem. More resources than ever are available in the area. The progress in the last 10 years, in part due to changes brought about by CaP CURE, is reason for hope. Nonetheless, while we are on the playing field, we cannot yet claim victory. The focus must be sustained, and the participation by government, industry, and the private sector needs to continue in order to maintain the momentum that has been created. It is our collective responsibility to accelerate this effort to eradicate prostate cancer as a health risk to men and their families. ■

Reference

1. Carter BS, Bova GS, Beaty TH, et al. Hereditary prostate cancer: epidemiological and clinical features. *J Urol*. 1993;150:797–802.